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Jon W Dudas

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

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INVENTOR(s)/APPLICANT(s)					
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TITLE OF THE INVENTION (280 characters max)					
COMPOUNDS AND METHODS FOR TREATING DYSLIPIDEMIA					
CORRESPONDENCE ADDRESS					
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,
SIGNATURE

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Date 10/08/03

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(if appropriate)

44,712

☐ Additional inventors are being named on separately numbered sheets attached hereto

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COMPOUNDS AND METHODS FOR TREATING DYSLIPIDEMIA**FIELD OF THE INVENTION**

The current invention relates to the fields of medicinal organic chemistry, pharmacology, and medicine. Further, the current invention relates to a group of compounds that demonstrate utility for treating pathological states due to dyslipidemia

BACKGROUND OF THE INVENTION

Coronary heart disease (CHD) is one of the major causes of morbidity and mortality worldwide. Despite attempts to modify risk factors such as obesity, smoking, lack of exercise, and treatment of dyslipidemia with dietary modification or drug therapy, CHD remains the most common cause of death in the U.S. Over 50% of all CHD deaths are due to underlying atherosclerotic coronary heart disease.

Dyslipidemia is a major risk factor for CHD. Low plasma levels of high density lipoprotein (HDL) cholesterol with either normal or elevated levels of low density (LDL) cholesterol is a significant risk factor for developing atherosclerosis and associated coronary artery disease in humans. Indeed, several studies on lipoprotein profiles of CHD patients have shown that about 50% of the CHD patients have cholesterol levels that are considered to be in the normal range (<200 mg/dl). Furthermore, these studies found low HDL cholesterol in about 40% of the normo-cholesterolemic CHD patients as compared to the general population reported in the National Health and Nutrition Examination

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Survey. Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of cardiovascular disease including, but not limited to, atherosclerosis, CHD, stroke, and peripheral vascular disease.

Cholesterol ester transfer protein (CETP) is a 74 KD glycoprotein that facilitates the exchange of cholesterol esters in HDL for triglycerides in triglyceride-rich lipoproteins (A. R. Tall et. al., (1999) 1999 George Lyman Duss Memorial Lecture: Lipid transfer proteins, HDL metabolism and atherogenesis. *Arterio. Thromb. Vasc. Biol.* 20:1185-1188.). The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be proatherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD. Niacin can significantly increase HDL, but has serious toleration issues that reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL cholesterol only modestly (~10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent which can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

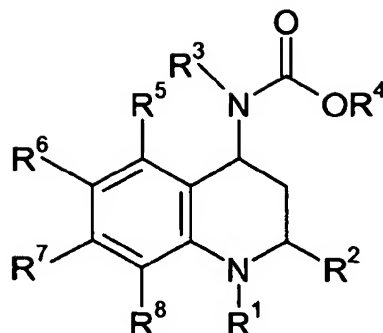
CETP is expressed in multiple tissues and secreted into plasma, where it associates with HDL (X.C. Jiang et. al., (1991) Mammalian adipose tissue and muscle are major sources of lipid transfer protein mRNA. *J. Biol. Chem.* 266:4631-4639). Humans and monkeys, which express CETP, have relatively low HDL cholesterol, whereas mice and rats do not express CETP and carry nearly all their cholesterol in HDL. Further more, transgenic expression of CETP in mice results in significantly reduced HDL cholesterol levels and developed severe atherosclerosis compared to control mice (K.R. Marotti et. al., (1993) Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein. *Nature*:364, 73-75). Expression of human CETP in Dahl salt-sensitive hypertensive rats led to spontaneous combined hyperlipidemia, coronary heart disease and decreased survival (V.L.M. Herrera et. al., (1999) Spontaneous combined hyperlipidemia, coronary heart disease and decreased survival in Dahl salt-sensitive hypertensive rats transgenic for human cholesteryl ester transfer protein. *Nature Medicine*: 5, 1383-1389).

Antibodies either directly injected into the plasma or generated through vaccine injection can effectively inhibit CETP activity in hamsters and rabbits resulting in elevated HDL cholesterol (C. W. Rittershaus, (1999) Vaccine-induced antibodies inhibit

CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. Furthermore, antibody neutralization of CETP in rabbits has been shown to be anti-atherogenic (*Arterio. Thromb. Vasc. Biol.* 20, 2106-2112; G.F. Evans et. al., (1994) Inhibition of cholesteryl ester transfer protein in normocholesterolemic and hypercholesterolemic hamsters: effects on HDL subspecies, quantity, and apolipoprotein distribution. *J. Lipid Research.* 35, 1634-1645). However, antibody and/or vaccine therapy is not currently a viable option for the treatment of large populations of patients in need of treatment for dilipidemia and resultant or associated disease state manifestations.

There have been several reports of small molecule CETP inhibitors. Barret et. al. (J. Am. Chem. Soc., 118, 7863, (1996)) and Kuo et al. (J. Am. Chem. Soc., 117, 10629, (1995)) describe cyclopropan-containing CETP inhibitors. Pietzonka et al. (Bioorg. Med. Chem. Lett. 6, 1951 (1996)) describe phosphonate-containing analogs as CETP inhibitors. Coval et al. (Bioorg. Med. Chem. Lett. 5, 605, (1995)) describe Wiedendiol-A and -B related sesquiterpenes as CETP inhibitors. Japanese Patent Application No. 10287662-A describes polycyclic, non-amine containing, polyhydroxylic natural compounds possessing CETP inhibition properties. Lee et al. (*J. Antibiotics*, 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids*, 25, 216-220 (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zillversmit (*J. Lipid Res.*, 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al. (*Biochem. Biophys. Res. Comm.* 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. Describe 1,3,5-triazines as CETP inhibitors (*Bioorg. Med. Chem. Lett.*, 6, 919-22 (1996)). Bisgaier et al. (*Lipids*, 29, 811-8 (1994)) describe 4-phenyl-5-tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor. Oomura et al. Disclose non-peptidic tetracyclic and hexacyclic phenols as CETP inhibitors in Japanese Patent Application No. 10287662.

United States patent No. 6,586,448 B1 describes 4-carboxamino-2-substituted-1,2,3,4-tetrahydroquinolines of formula I



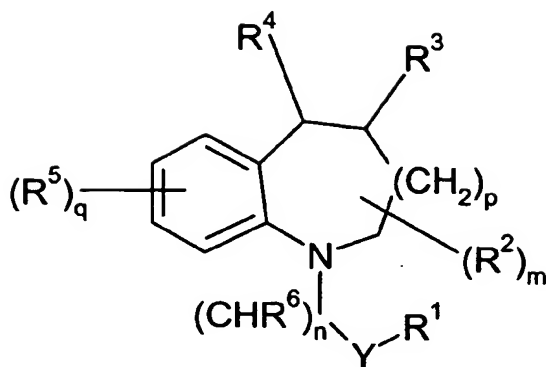
and prodrugs thereof, and pharmaceutically acceptable salts of said compounds and said prodrugs; wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined therein. Similarly, PCT patent applications WO 03/063868A1, WO 0017164, No.0017165, and WO 0017166, discloses variously, formulations, methods of preparation and methods of use of compounds tetrahydroquinoline compounds generally related to that of U.S patent 6,586,448 B1 from which it derives or is a divisional application thereof.

European Patent Application No. 818448 by Schmidt et al. describes tetrahydroquinoline derivatives as cholesteryl ester transfer protein inhibitors. European Patent Application No. 818197, Schmek et al. describe pyridines with fused heterocycles as cholesteryl ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430 describe bicyclic condensed pyridine derivatives as cholesteryl ester transfer protein inhibitors. In US Patent 6,207,671 Schmidt et al. describe substituted pyridine compounds as CETP inhibitors. In WO Patent Application No. 09839299, and WO Patent application No.03028727 by Muller-gliemann et al. and Erfinder/Anmelder respectively, describe quinoline derivatives as cholesteryl ester transfer protein inhibitors.

The above disclosures notwithstanding, a great need remains, particularly for affluent western societies for effective compounds useful to treat conditions caused by, associated with or exacerbated by dyslipidemia.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



wherein

n is 0, 1, 2, or 3;

m is 0, 1, 2, or 3;

p is 1 or 2;

q is 0, 1, 2, or 3;

Y is a bond, $C=O$, or $S(O)_p$

R^1 is selected from a group consisting of hydroxy, C_1 - C_6 alkyl, aryl, C_2 - C_6 alkenyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylheterocyclic, C_3 - C_8 cycloalkyl, C_1 - C_6 alkylaryl, heterocyclyl, C_1 - C_6 alkoxy, aryloxy, $-OC_2$ - C_6 alkenyl, $-OC_1$ - C_6 haloalkyl, $-OC_1$ - C_6 alkylheterocyclic, $-OC_3$ - C_8 cycloalkyl, $-NR^7R^8$ and $-OC_1$ - C_6 alkylaryl, $-O$ -heterocyclic, and $-OC_1$ - C_6 alkylheterocyclic; provided that R^1 is not hydroxy when Y is $S(O)_p$;

R^2 is bound only to carbon atoms and is a group independently selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, heterocyclyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl; wherein the alkyl group is optionally substituted by alkyloxy, aryloxy, haloalkyl, heterocyclyl;

R^3 is hydrogen or a group represented by the formula $-NR^9R^{10}$;

R^4 is hydrogen or a group represented by the formula $-NR^9R^{10}$; provided that R^3 and R^4 are not simultaneously hydrogen or $-NR^9R^{10}$;

R^5 is selected from a group consisting of hydrogen, hydroxy, C_1 - C_6 haloalkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 alkylaryl, C_1 - C_6 alkylheterocyclic, aryl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, aryloxy, $-OC_2$ - C_6 alkenyl, $-OC_1$ - C_6 haloalkyl, $-NR^7R^8$, and $-OC_1$ - C_6 alkylaryl wherein C_1 - C_6 alkyl is optionally substituted by alkyloxy, aryloxy;

R^6 is independently selected from a group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl hydroxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, aryloxy, $-OC_2$ - C_6 alkenyl, $-OC_1$ - C_6 haloalkyl, C_1 - C_6 alkyl NR^7R^8 , C_3 - C_8 cycloalkyl, and C_1 - C_6 alkylcycloalkyl; R^7 and R^8 are independently selected from a group consisting of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_3 - C_8 cycloalkyl, heterocyclic, aryl, C_1 - C_6 alkylaryl, wherein each alkyl, or aryl group is optionally substituted with 1-3 groups independently selected from halogen, C_1 - C_6 alkylheterocyclic, C_1 - C_6 haloalkyl, and $NR^{11}R^{12}$, or R^7 and R^8 combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional hetero-atoms selected from oxygen, nitrogen or sulfur and may be optionally substituted with oxo, or C_1 - C_6 alkyl;

R^9 is the group COR^7 or $S(O)_pR^7$ wherein R^7 is as defined above.

R^{10} is selected from the group consisting of C_1 - C_6 alkylaryl, C_2 - C_6 alkenylaryl, C_2 - C_6 alkynylaryl, C_1 - C_6 alkylheterocyclic, C_1 - C_6 alkylcycloalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl- O - C_1 - C_6 alkylaryl, C_1 - C_6 alkyl- NR^2 - C_1 - C_6 alkylaryl, aryl, and wherein each alkyl, alkenyl, cycloalkyl, aryl, or heterocyclic group are optionally substituted with 1-3 groups independently selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, C_1 - C_6 haloalkyl, halogen, C_1 - C_6 alkoxy, aryloxy, C_1 - C_6 alkenyloxy, C_1 - C_6 haloalkoxyalkyl, NR^7R^8 and $-OC_1$ - C_6 alkylaryl;

R^{11} and R^{12} are independently selected from a group consisting of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_3 - C_8 cycloalkyl, heterocyclic, aryl, C_1 - C_6 alkylaryl, wherein each aryl group is optionally substituted with 1-3 groups independently selected from halogen, C_1 - C_6 alkylheterocyclic, and C_1 - C_6 haloalkyl, or R^{11} and R^{12} combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen or sulfur and is optionally substituted with oxo, or C_1 - C_6 alkyl; or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

The present invention also provides a method for modulating CETP activity comprising the use of a compound of formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof, for the treatment, prevention or amelioration of CETP mediated diseases.

The present invention provides a method for treating or preventing dyslipidemia comprising administering a compound of formula I, pharmaceutically acceptable salt,

solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating or preventing CHD comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating and/or preventing atherosclerosis comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating and/or preventing diseases related to abnormal CETP activity comprising administering a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of raising the ratio of plasma HDL-cholesterol to plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of raising the level of plasma HDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of lowering the level of plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof, and a carrier.

The present invention also provides a method of treating and/or preventing the pathological sequelae due to low levels of plasma HDL and/or high levels of LDL-

cholesterol in a mammal comprising administering an effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers, thereof, to a patient in need thereof.

The present invention also relates to the use of a compound of formula I for the manufacture of a medicament for treating and/or preventing atherosclerosis in a mammal comprising administering an effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention also provides a combination therapy involving a compound of formula I and one or more other cardio protective agents such as for example, statins, leptin, and/or other LXR, CETP, ABC A1 or lipid regulating agents useful for the treatment and/or prevention of atherosclerosis.

DETAILED DESCRIPTION OF THE INVENTION

The current invention provides novel compounds of formula I useful in modulating CETP activity.

The term "modulation" would include, but not be limited to, up-regulation, down-regulation, inhibition, agonism, antagonism of the CETP receptor as appropriate to achieve HDL raising, or LDL lowering and the resulting biological sequelae from such intervention.

The phrase "diseases" or "diseases related to CETP modulation" or "diseases mediated by CETP activity" refers to pathological states where atherosclerosis and cardiovascular diseases are prone because of dyslipidemia and/or other risk factors and are therefore beneficially affected by down-regulation (modulation) of CETP activity. These diseases include but are not limited to hyperlipidemia and its sequelae such as atherosclerosis, CHD, elevated blood pressure, CHF, stroke, hypertension, hypertriglyceremia, diabetes, obesity, inflammatory diseases including but not limited to dermatitis, arthritis, and pain, and diseases of the central nervous system including but not limited to dementia, cognitive disorders such as Alzheimer's disease.

The term "treatment" bears its usual meaning which includes prohibiting, inhibiting, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of a pathological symptom related to or resultant from the

modulation of CETP activity, especially as related to raising plasma levels of HDL, or lowering LDL-cholesterol levels or raising the HDL/LDL ratio or controlling atherosclerosis, hyperlipidemia and/or hypercholesterolemia.

Generally, one of skill in the art is aware that valency must be conserved (complete) for all stable molecules. Therefore, the necessary implication that hydrogen atoms are necessary and available to complete valency in all structures including formula I unless expressly indicated otherwise, is imputed to the general knowledge of one of skill in the art.

General chemical terms used in the description of compounds herein described bear their usual meanings. For example, the term "C₁₋₆ alkyl," or "(C₁₋₆)alkyl" or "C₁₋₆ alkyl" refers to a straight or branched aliphatic chain of 1 to 6 carbon atoms including but not limited to methyl, ethyl, propyl, iso-propyl, n-butyl, pentyl, and hexyl. Unless otherwise stated, the term "alkyl" means C₁₋₆ alkyl. Similarly, the term "C₀₋₆ alkyl" implies an alkyl group as indicated wherein when the term C₀ applies, the alkyl group is not present, and the remaining groups attach directly to the substrate. The invention also contemplates that the term C₁₋₆ alkyl or C₂₋₆ alkenyl or similar terms also encompass the specified alkyl or alkenyl or similar group, which may be chiral, regio or stereoisomeric. Such chiral or regio or stereoisomeric groups are also objects of the present invention.

The term alkylaryl refers to an alkyl group substituted by an aryl group. For example, C₁₋₆ alkylaryl indicates that a C₁₋₆ alkyl group is attached to the aryl group, and that the resulting C₁₋₆ alkylaryl is attached to the nucleus via the alkyl group. A most preferred alkylaryl group is benzyl.

The term "substituted phenyl" or "optionally substituted phenyl" refers to a phenyl group having one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy, -COOR¹, C₀₋₆ alkylNR¹R², nitro, chloro, fluoro, bromo, iodo, C₁₋₆haloalkyl, C₁₋₆ haloalkoxyalkyl, C₀₋₆ alkylheterocyclic.

The term "aryl" refers to a substituted or unsubstituted aromatic or heteroaromatic carbocyclic or heterocyclic radical selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 2-benzofuryl, 3-benzofuryl, 4-benzofuryl, 5-benzofuryl, 6-benzofuryl, 7-benzofuryl, 2-benzothiényl, 3-benzothiényl, 4-benzothiényl, 5-

benzothienyl, 6-benzothienyl, 7-benzothienyl, 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl and 7-indolyl. As used herein the term aryl also encompasses the benzyl group.

The term "C₃-C₈ cycloalkyl" or similar terms refer to a saturated carbocyclic ring having from 3 to 8 carbon atoms.

The term "carbocycle" as used herein refers to a cyclic group having only carbon and appropriate number of hydrogen atoms. The term encompasses groups such as cycloalkyl, cycloalkene, cycloalkylene, naphthyl, phenyl and the like.

The term "heterocycle", "heterocyclyl", or "heterocyclic" refers to a 5, 6 or 7 member saturated, partially unsaturated, or aromatic mono-cyclic or a benzofused bicyclic ring containing 1-5 heteroatoms selected from N, S or O, wherein said heterocycle is optionally substituted at carbon or nitrogen atom(s) unless otherwise specified. Most preferred heterocyclic groups include pyrrolidinyl, piperidinyl, hexamethyleneimino, morpholino, benzthiophene, indolyl, quinolyl, isoquinolyl, tetrazolyl, and pyridinyl. As a corollary, the term "alkylheterocyclic" or "alkylheterocycle" is understood to mean that the alkyl group is attached to the heterocycle and the point of attachment to the molecular backbone or nucleus is the alkyl group.

The term "haloalkoxyalkyl" as used herein include for example trifluoromethoxy, pentafluoroethoxy, trifluoroethoxy (OCH₂CF₃) and the like.

The term "Prodrugs" describes derivatives of the compounds of the invention that have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives, such as, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic esters (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl) or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. Other preferred esters include morpholinoethyloxy, diethylglycolamide and diethylaminocarbonylmethoxy. In

some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters.

As used herein, the term "protecting group" refers to a group useful for masking reactive sites in a molecule to enhance the reactivity of another group or allow reaction at another desired site or sites following which the protecting group may be removed.

Protecting groups are usually used to protect or mask groups including but not limited to -OH, -NH, and -COOH. Suitable protecting groups are known to one of skill in the art and are described in *Protecting groups in Organic Synthesis*, 3rd edition, Greene, T. W.; Wuts, P.G.M. Eds., John Wiley and Sons, New York, 1999.

As used herein, the term "solvate" is a form of the compound of the invention wherein a crystal or crystals of a compound of the invention have been formed from a stoichiometric or non-stoichiometric amount of the compound of formula I and a solvent. Typical solvating solvents include for example, water, methanol, ethanol, acetone and dimethylformamide.

In those instances where a compound of the invention possesses acidic or basic functional groups, various salts may be formed which are more water soluble and/or more physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion-exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base or acid addition salts of compounds of the present invention. Base addition salts include for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, hydrobromide, camsylate, carbonate, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrochloride, hydroxynaphthoate, hydroiodide,

isothionate, lactate, lactobionate, laureate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Preferred salts for the purpose of the invention include the hydrochloride salt, the hydrobromide salt, the bisulfate salt, the methane sulfonic acid salt, the *p*-toluenesulfonic acid salt, bitartrate, the acetate and the citrate salt.

A compound of the invention as illustrated by formula I may occur as any one of its positional isomers, stereochemical isomers or regio-isomers, all of which are objects of the invention. Certain compounds of the invention may possess one or more chiral centers, and thus, may exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group, there exist the possibility of *cis*- and *trans*-isomeric forms of the compounds. The *R*- and *S*- isomers and mixtures thereof, including racemic mixtures as well as mixtures of enantiomers or *cis*- and *trans*- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereo-specific reactions with starting materials that contain the asymmetric centers and are already resolved. Alternatively desired stereoisomers may be prepared by methods that lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound i.e. a chiral resolving agent. This changes the racemic form into a mixture of stereoisomers and diastereomers, because they have different melting points, different boiling points, and different solubilities and can be separated by conventional means, such as crystallization.

Preferred Embodiments of The Invention

Preferred *n*, *m*, *p*, and *q*

Preferably *n* is 0, or 1. More preferably, *n* is 0.

Preferably *m* is 0, or 1.

Preferably *p* is 1, or 2.

Preferably, q is 0, 1 or 2. More preferably q is 1 or 2. Most preferably, q is 1.

Preferred R¹

A preferred R¹ groups is selected from the group consisting of aryloxy, -OC₁-C₆ haloalkyl, -OC₁-C₆ alkylcycloalkyl, -OC₁-C₆ alkylcycloalkylNR⁷R⁸, C₁-C₆ alkoxy, -OC₁-C₆ alkylaryl, and -OC₁-C₆ alkylheterocyclic. More preferred is an R¹ group selected from C₁-C₆ alkoxy, -OC₁-C₆ alkylaryl, and -OC₀-C₆ alkylcycloalkylNR⁷R⁸. Most preferred is an R¹ group represented by C₁-C₆ alkoxy.

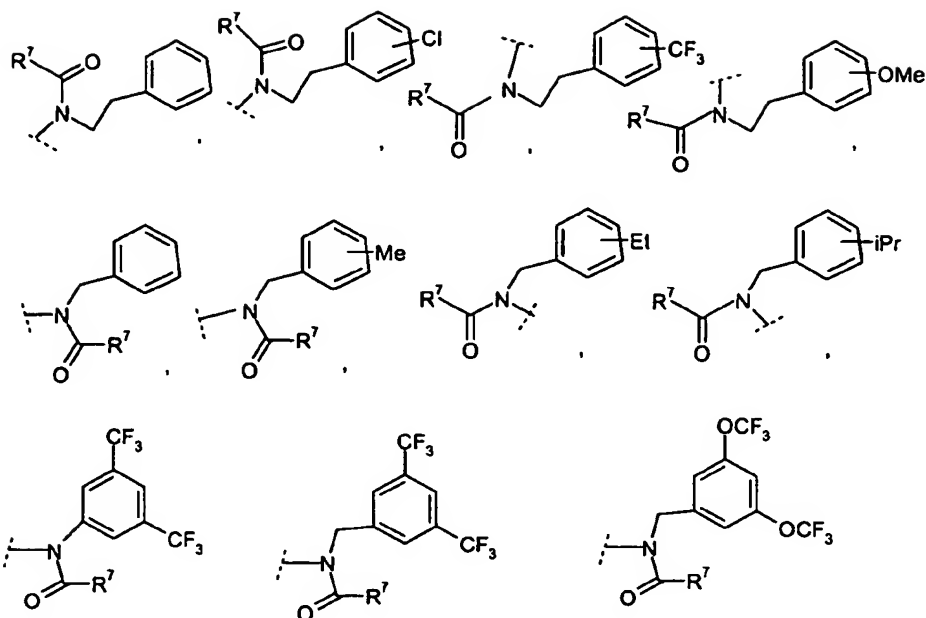
Preferred R²

A preferred R² groups is selected from the group consisting of hydrogen, hydroxy, C₁-C₆ haloalkyl, C₁-C₆ alkyl, halo, C₁-C₆ alkylhalide, -OC₁-C₆ alkyl, -OC₁-C₆ haloalkyl, -OC₁-C₅ alkylcycloalkyl, C₀-C₆ alkylNR⁷R⁸, -OC₁-C₆ alkylaryl, and -OC₁-C₆ alkylheterocyclic. More preferred is an R² group selected from hydroxy, C₁-C₆ alkyl, halo C₁-C₆ alkylhalide and C₁-C₆ alkoxyalkyl. Most preferred is an R² group represented by hydrogen or C₁-C₆ alkyl.

Preferred R³ and R⁴ Groups

Preferred R³ and R⁴ are selected from hydrogen or a group represented by the formula —NR⁹R¹⁰, provided that R⁹ and R¹⁰ are not simultaneously hydrogen.

More preferably, the group —NR⁹R¹⁰, represents R³ and R⁴ is hydrogen. More preferably, the group —NR⁹R¹⁰ is represented by a group selected from the group consisting of:



Preferred R^5 and R^6 groups

R^5 is preferably selected from a group consisting of hydrogen, hydroxy, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, aryloxy, $-OC_2$ - C_6 alkenyl, $-OC_1$ - C_6 haloalkyl, $-CH_2NR^7R^8$, $-NH_2$, $-CN$, $-COOH$, and NO_2 ;

R^6 is at each occurrence independently selected preferably from a group consisting of hydrogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy.

Preferred R^7 and R^8

Preferred R^7 and R^8 are independently selected from a group consisting of C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkylaryl, and C_1 - C_6 alkylheterocyclic, wherein each aryl group is optionally substituted with 1-3 groups independently selected from C_1 - C_6 alkyl, halo, and C_1 - C_6 haloalkyl.

Preferred R^{11} and R^{12}

Preferred R^{11} and R^{12} are independently selected from a group consisting of C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkylaryl, and C_1 - C_6 alkylheterocyclic, wherein each aryl group is optionally substituted with 1-3 groups independently selected from C_1 - C_6 alkyl, halo, and C_1 - C_6 haloalkyl.

A most preferred compound of the invention is a compound selected from the group consisting of:

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-bromo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-bromo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-bromo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-methoxy-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-fluoro-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,4-dimethyl-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

6-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-trifluoromethyl-3,4,5,6-tetrahydro-2H-benzo[b]azocine-1-carboxylic acid isopropyl ester,

6-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-9-trifluoromethyl-3,4,5,6-tetrahydro-2H-benzo[b]azocine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-9-trifluoromethyl-3,4,5,6-tetrahydro-2H-benzo[b]azocine-1-carboxylic acid isopropyl ester,
4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-chloro-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-8-chloro-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester, or a pharmaceutically acceptable salt, solvate enantiomer or diastereomer or mixture thereof.

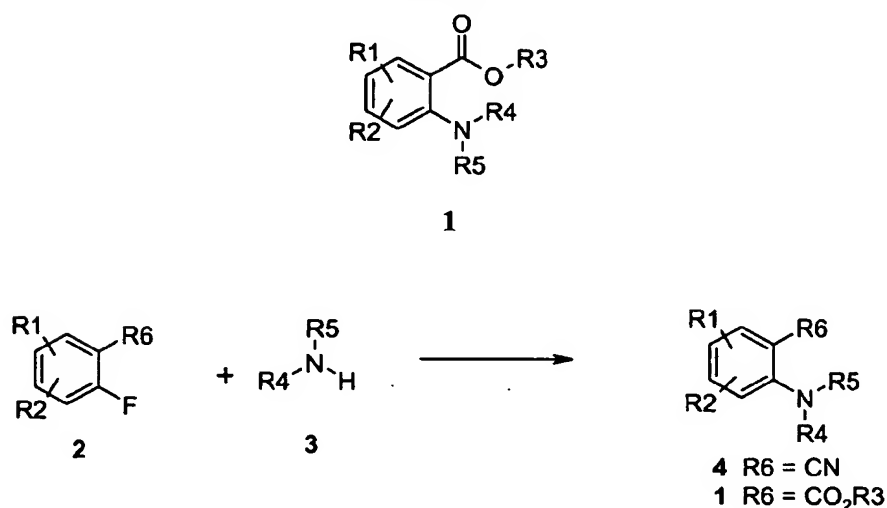
The geometric isomers associated with the asymmetric carbon atoms of compounds of formula I are also contemplated to be within the scope of the current invention as useful for the treatment of diseases related to CETP modulation.

Synthesis of Compounds of the Invention

The compounds of the instant invention can be synthesized as exemplified in Schemes 1 – 12. Anthranilate intermediates of Formula 1 can be chemically prepared, for example, by following the synthetic routes set forth in the Schemes below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art. Other necessary reagents and starting materials may be made by procedures which are selected from standard techniques of organic and heterocyclic chemistry, techniques which are analogous to the syntheses of known structurally similar compounds, and the procedures described in the Preparations and Examples below, including any novel procedures. This includes, but is not limited to, esterification of a carboxylic acid, hydrolysis of a nitrile to a carboxylic acid, and subsequent esterification. In addition, one of ordinary skill will appreciate that many of the necessary reagents or starting materials can be readily obtained from commercial suppliers. The R, R1, R2, R3, R4, R5, R6, etc, used within this section for the purpose of illustrating the various methods

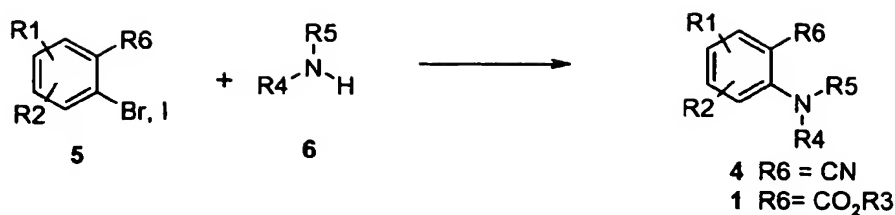
of synthesizing compounds of the invention are not necessarily synonymous in scope or meaning with similar groups used in the generic structure for compounds of formula I. However, groups in similar positions are co-extensive in scope and meaning compared to groups occupying similar positions as defined for the generic structure of compounds of formula I.

Scheme 1



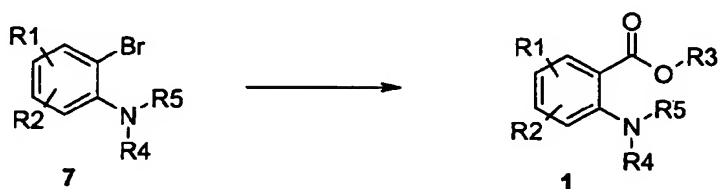
In Scheme 1, the nucleophilic aromatic substitution occurs by methods known in the art, (Wells, K. M. et al. Tetrahedron Letters, 1996, 37(36), 6439-6442). The appropriately substituted amine is dissolved in a suitable solvent, such as DMF or DMSO, with a base, such as cesium carbonate, and the appropriately substituted fluoro benzoate or benzonitrile (R6 = CN or CO₂R₃). The reaction proceeds at 0°C to elevated temperatures in anywhere from ten minutes to several days depending on the stability of the starting materials. The product of structure 4 (R6 = CN) or 1 (R6 = CO₂R₃) can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Scheme 2



In Scheme 2, the N-Aryl coupling occurs by methods known in the art, (Hartwig, J. F. et al. *Angew. Chem., Int. Ed. Engl.* 1998, 37, 2046-2067). The appropriately substituted amine is dissolved in a suitable solvent, such as DMF, with a base, such as cesium carbonate or sodium *tert*-butoxide, the appropriately substituted halogenated benzoate or benzonitrile (R6 = CN or CO₂R3), and a suitable catalyst complex, such as palladium acetate and diphenyl phosphino ferrocene. The reaction proceeds at 0°C to elevated temperatures in anywhere from ten minutes to several days depending on the stability of the starting materials. The product of structure 4 (R6 = CN) or 1 (R6 = CO₂R3) can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

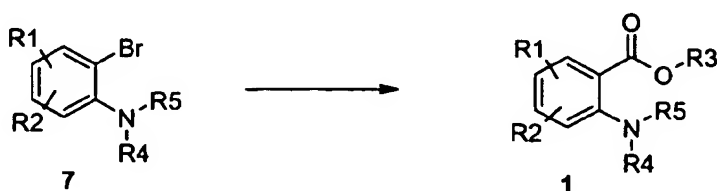
Scheme 3



In Scheme 3, the carbonylation occurs by methods known in the art, (Heck, *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, p. 348-358). The appropriately substituted aryl bromide is dissolved in a suitable solvent, such as DMF, with a base, such as cesium carbonate or sodium *tert*-butoxide, and a suitable catalyst complex, such as palladium acetate and diphenyl phosphino ferrocene, appropriate alcohol (R3-OH) and saturated with carbon monoxide. The reaction proceeds at 0°C to

elevated temperatures in anywhere from ten minutes to several days depending on the stability of the starting materials. The product of structure 1 may then be isolated by a standard aqueous workup, optionally followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Scheme 4

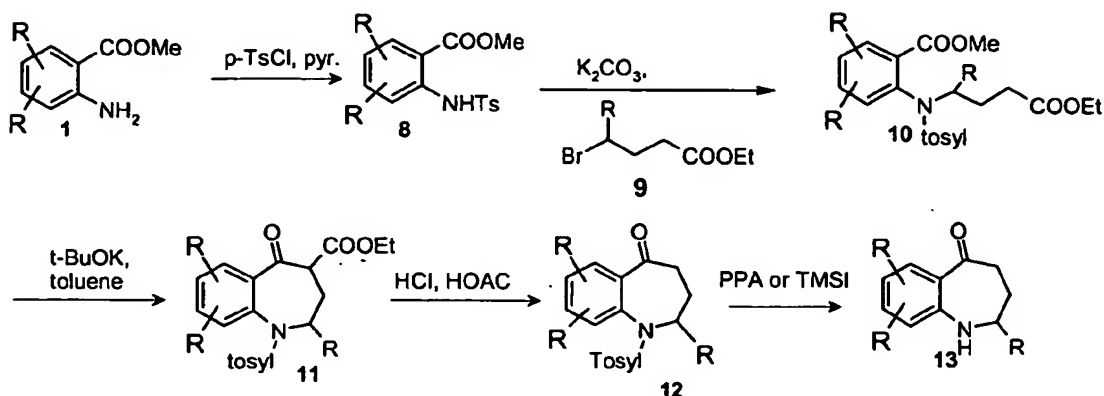


In Scheme 4, the aromatic carboxylation occurs by methods known in the art, (Boger, D. L. et al, *Journal of Organic Chemistry*, 1994, 59(17), 4943-4949, Volpin et al, *Organomet. Reactions*, 1975, 5, 313-386). The appropriately substituted aryl bromide is dissolved in a suitable solvent, such as diethyl ether or tetrahydrofuran, with an alkyl lithium, such as *n*-butyl lithium or *tert*-butyl lithium or magnesium turnings. The resulting anion is quenched with a suitable carbon dioxide source, such as dry ice, or dimethyl carbonate. The reaction proceeds at -78°C to room temperature in anywhere from about five minutes to several hours depending on the stability of the starting materials. The product of structure 1 can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Synthetic Scheme 5 shows preparation of the benzazepine intermediates, which are intermediates for compounds on the invention depicted by Formula 1. For example, substituted anthranilic esters 1 that are either commercially available or prepared as set forth in the literature or in schemes 1-4, can be *N*-sulfonylated to provide 8, which in turn may be alkylated with appropriately substituted, or unsubstituted 3-bromopropanoic acid esters 9 thus affording 10. Dieckmann condensation cyclization of intermediate 10 yields *N*-tosyl benzazepine 11 which is subjected to acid hydrolysis and decarboxylation to give benzodiazepin-5-one derivatives 12. Removal of tosyl group with either acid (e.g. PPA

(polyphosphoric acid)) or TMSI (trimethylsilyliodide) provides intermediate benzazepine-5-one 13.

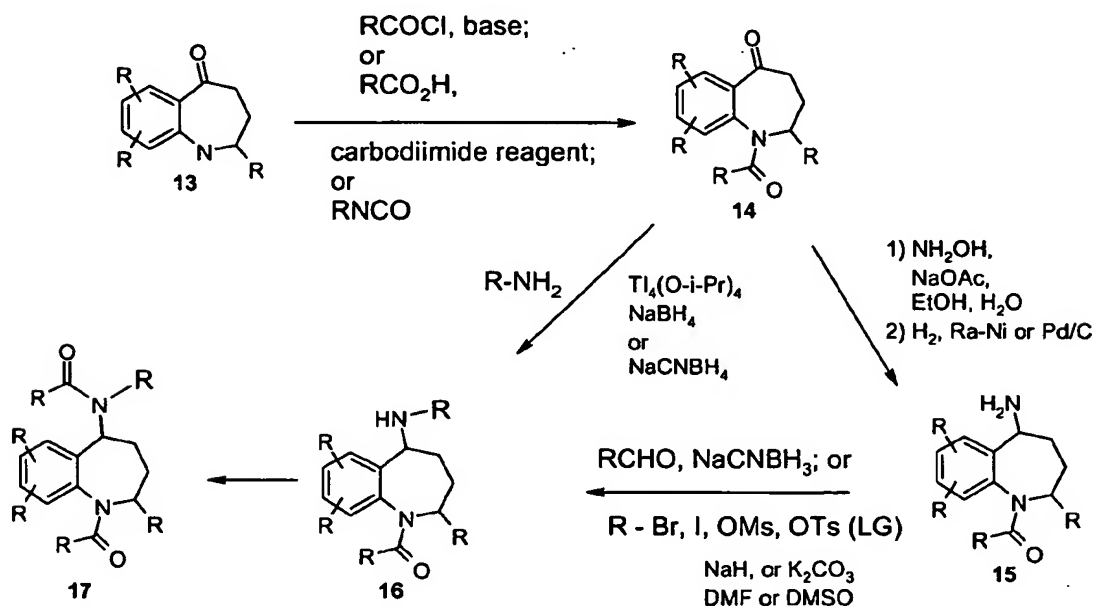
Scheme 5



Benzazepine-5-ones of general structure 13 are converted to compounds of formula I utilizing the steps outlined in Scheme 6. N-acylation of 13 to afford carbamates of structure 14 is accomplished by treatment with an appropriately substituted aryl or alkyl chloroformate in the presence of an organic base such as pyridine. Alternatively, treatment with an acid chloride or an appropriate activated ester, such as those generated *in-situ* from the reaction of an appropriately substituted aryl or alkyl carboxylic acid Generation of urea derivatives from 13 is accomplished by treatment with a carbamoyl chloride in the presence of base such as pyridine and DMAP (dimethylamino pyridine) or an alternative base such as NaH in DMF. Alternatively treatment with phosgene, or carbodiimide (CDI) reagent such as cyclohexylcarbodiimide or analog thereof, followed by the addition of an appropriately di-substituted amine will afford ureas of structure 14. Formation of sulfonamide derivatives from 13 can be accomplished by reaction with appropriately substituted sulfonyl chlorides in the presence of base. Conversion of ketone 14 to 17 may be performed either through direct reductive amination with an appropriately substituted alkyl or aryl amine to directly afford 16, or alternatively through formation of the amine derivate 15 by reduction of an intermediate oxime, followed by alkylation with an appropriately substituted benzylic halide, mesylate or tosylate, or reductive alkylation with the appropriate aldehyde or ketone in the presence of a reducing reagent such as NaCNBH₃. 16 is converted to 17 (a compound of the invention) by

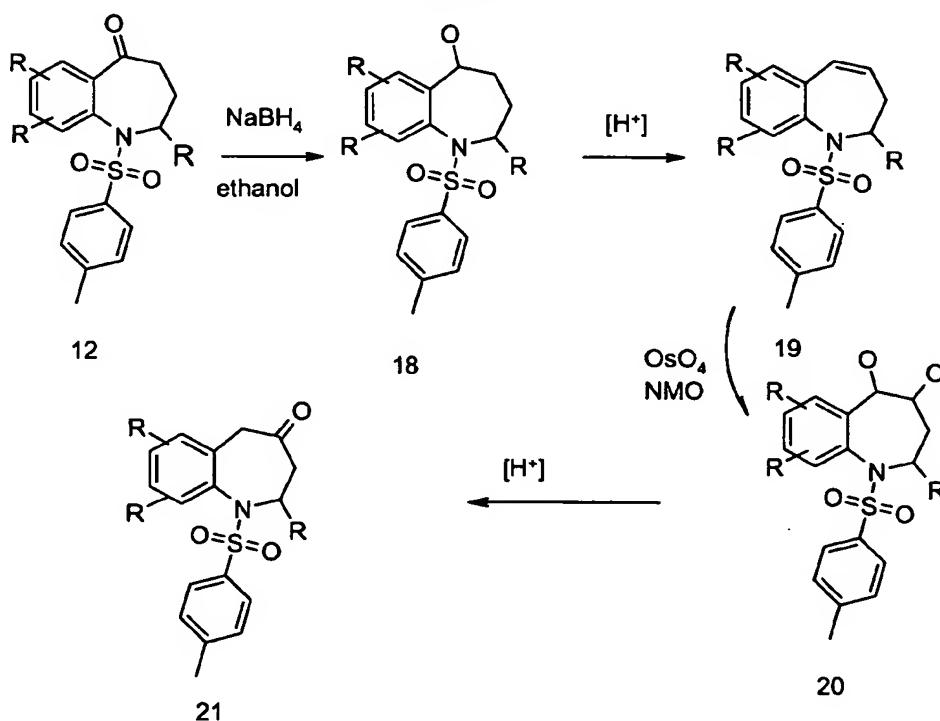
acylation with an appropriately substituted symmetrical anhydride or acid halides to afford amides, or chloroformates to afford carbamates, or isocyanates, carbamoyl chlorides, etc. to form ureas, or appropriately substituted sulfonyl chlorides to afford sulfonamides.

Scheme 6



N-tosyl Benzazepine-5-ones of general structure **12** are converted to compounds of general structure **21** utilizing the steps outlined in Scheme 7. Reduction of the ketone can be effected using a variety of reducing agents such as sodium borohydride to yield compound **18**. This compound can then be eliminated to the olefin via an acid catalyzed procedure known to one of skill in the art to afford **19**. The olefin can then be oxygenated to the diol **20** in a variety of ways such as the use of a catalytic amount of osmium tetroxide with N-methyl morpholine oxide. This diol can then be converted to compound **21** by treatment with an appropriate acid to eliminate the benzyl alcohol and tautomerize to the ketone. *c.f.*: Burnell, R.H., Jean, M; *Synthetic Communications*, 14(13), 1229-1237 (1984).

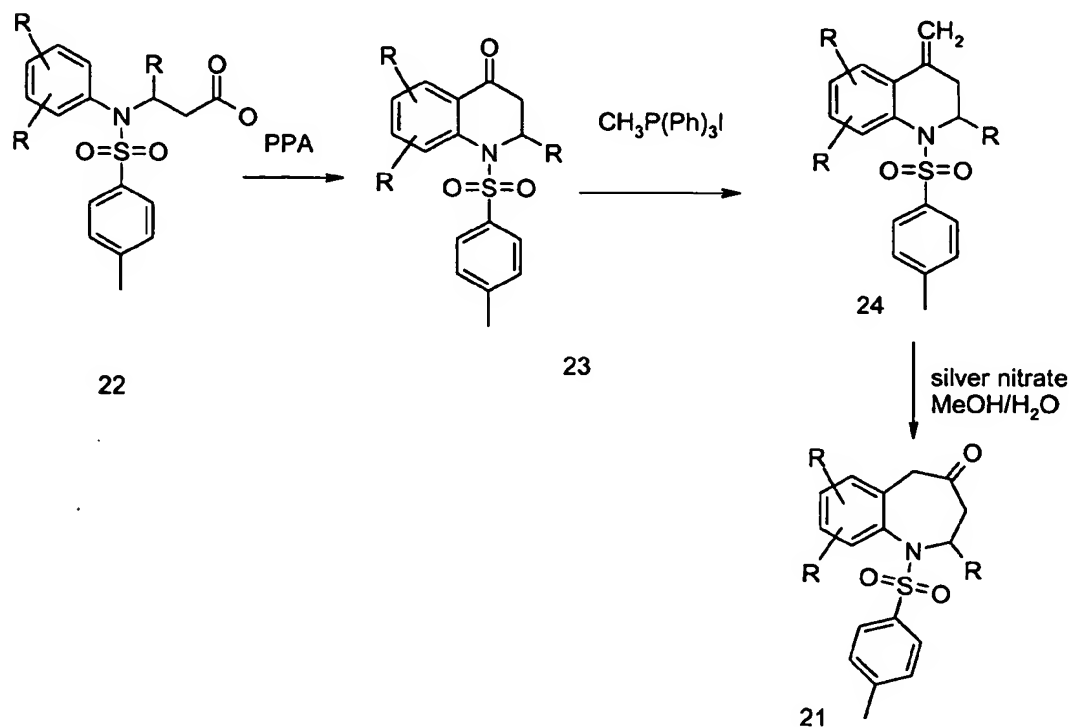
Scheme 7



Alternatively the ketone **21** may be made via scheme 8 (Booker-Milburn, K.I., et al.; *J. Chem. Soc., Perkin Trans. 1*, 3261-3273 (1997)). N-(*p*-tolylsulfonyl)-3-aminopropanoic acids can be made by alkylation of the appropriate aniline via the same procedure shown in scheme 1 (compound **4**) and then saponification of the ester to yield

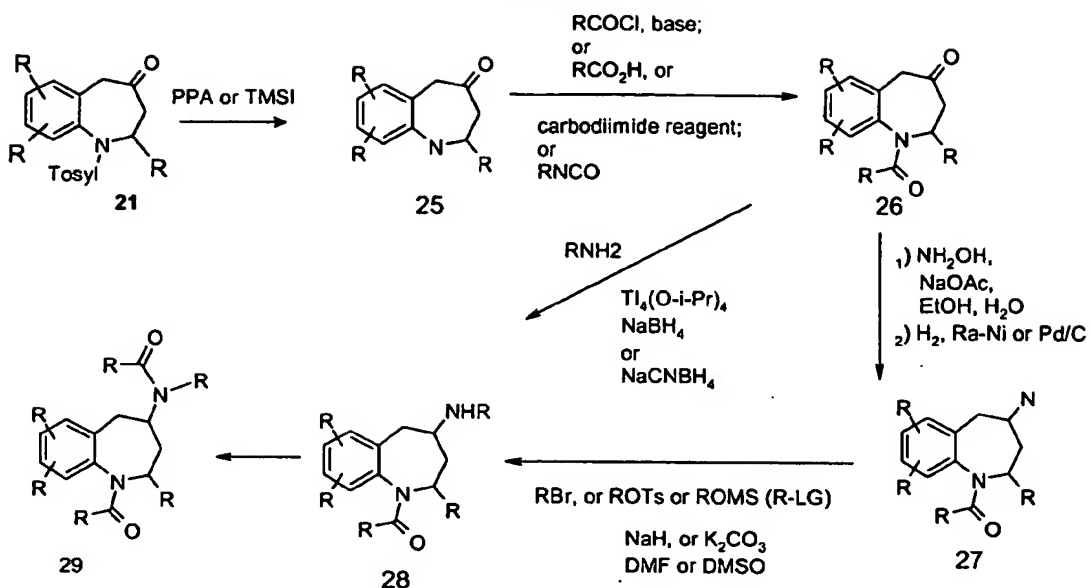
compound **6b**. This compound can then undergo an intermolecular acylation to form the 4-keto quinoline **7b** using a variety of procedures known in the art. Wittig reaction of this compound with methyltriphenylphosphonium iodide will generate the olefin **8b**. Then by use of silver nitrate, this olefin will be converted to the desired ketone **5b**.

Scheme 8



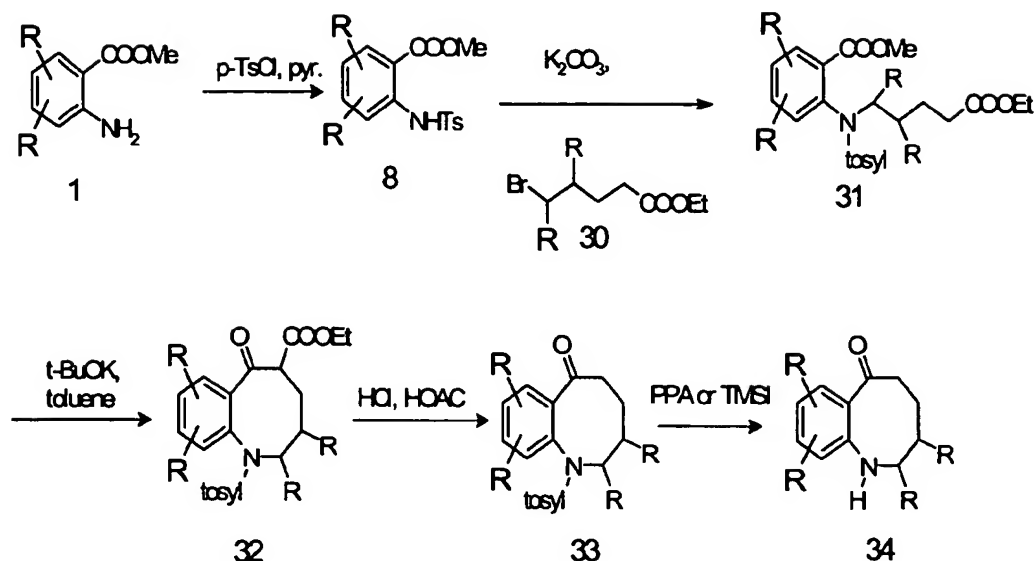
As show in scheme 9, Intermediates of general structure **21** are converted to **29** (a compound of the invention) utilizing the steps in a manner similar to that described for Scheme 6.

Scheme 9



Scheme 10 shows, for example, the synthesis of intermediates used for the preparation of 1-benzazacines of Formula I. For example, tosylation of **1** to give **8**, followed by alkylation with **30** provides **31**. Deickmann cyclization (Leonard, et al.: *J. Org. Chem.*, 1969, **34**, 1066) of **31** provides 1-benzazacin-6-one **32** which is further elaborated to **34** after decarboxylation and tosylate removal.

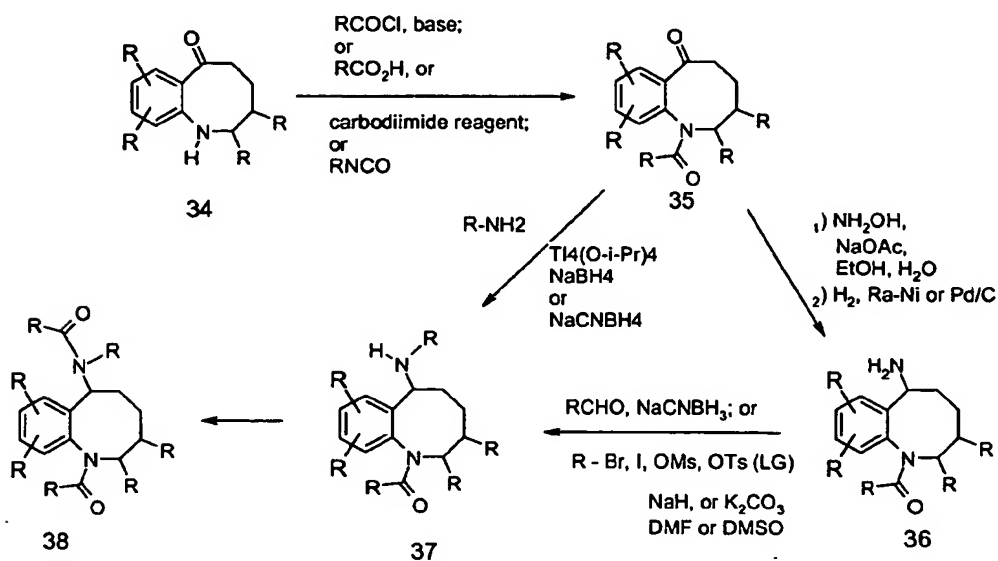
Scheme 10



1-Benzazacin-6-one compounds of general structure **34** are converted to compounds of formula I (**38**) utilizing the steps outlined in Scheme 11. N-acylation of **34** to afford carbamates of structure **35** is accomplished by treatment with an appropriately substituted aryl or alkyl chloroformate in the presence of an organic base such as pyridine. Alternatively, treatment with an acid chloride or an appropriate activated ester, such as those generated *in situ* from the reaction of an appropriately substituted aryl or alkyl carboxylic acid. Generation of urea derivatives from **34** is accomplished by treatment with a carbamoyl chloride in the presence of base such as pyridine and DMAP or an alternative base such as NaH in DMF. Alternatively treatment with phosgene, or CDI, or an analog thereof, followed by the addition of an appropriately di-substituted amine will afford ureas of structure **35**. Formation of sulfonamide derivatives from **34** can be accomplished by reaction with appropriately substituted sulfonyl chlorides in the presence of base. Conversion of ketone **35** to **38** can be performed either through direct reductive amination with an appropriately substituted alkyl or aryl amine to directly afford **37**, or alternatively through formation of the amine derivative **36** by reduction of an intermediate oxime, followed by alkylation with an appropriately substituted benzylic halide, mesylate or tosylate, or reductive alkylation with the appropriate aldehyde or ketone in the presence of a reducing reagent such as NaCNBH₃. **37** is converted to **38** (a compound of the invention) by acylation with and appropriately substituted symmetrical anhydride or acid

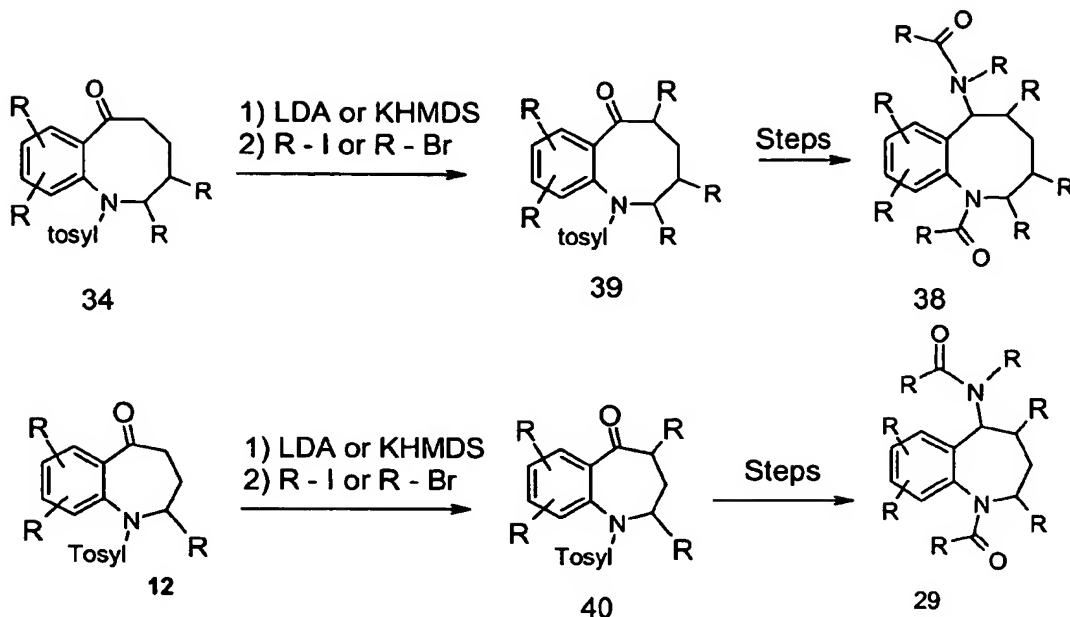
halides to afford amides, or chloroformates to afford carbamates, or isocyanates, carbamoyl chlorides, etc. to form ureas, or appropriately substituted sulfonyl chlorides to afford sulfonamides.

Scheme 11



Installation of substituents alpha-to the carbonyl of 1-Benzazacin-6-one **34**, or 1-Benzazapin-5-one **12** can be accomplished for example according to the method outlined in scheme 12 by enolate formation followed by alkylation with an appropriate alkyl halide. Conversion of **39** to **38** is as described, for example in Scheme 11. Conversion of **40** to **29** is as described, for example in Scheme 6.

Scheme 12



ASSAY

The following assay protocol and result(s) thereof demonstrating the utility and efficacy of the compounds and/or methods of the current invention are given for the purpose of illustration and are not meant to be limiting in any way.

IN VITRO CETP INHIBITOR ASSAY: SPA ASSAY

An in vitro Scintillation proximity assay (SPA) has been used to test the ability of compounds of this invention to inhibit the transfer of radiolabeled cholesterol esters between HDL and LDL. This assay monitors the inhibition of the transfer of [³H]cholesterol esters from HDL (Amersham) to biotinylated LDL (Amersham) by a CETP source. CETP produced by AV-12 cells that have been created to express human CETP has been used to mediate the transfer. After 30 minutes incubation in which the radiolabeled cholesterol ester is transferred in a HEPES-NaCl based buffer, the reaction is stopped and the biotinylated LDL is bound to streptavidin/scintillant coated SPA beads (Amersham). Then the radioactive signal has been measured in a Packard 96-well

scintillation TopCounter with window settings fully open. A decrease in radioactive signal represents the ability of compounds of the invention to inhibit the activity of CETP.

Alternatively, additional CETP sources can be used to mediate the transfer of radiolabeled cholesterol ester in this assay. Endogenous CETP from human plasma, CETP from mice made to express human CETP, and endogenous CETP from hamsters can be used as the CETP source in this assay.

Alternatively, other sources may be used as the buffer. In addition to the HEPES-NaCl based buffer that has been used in this assay, human plasma, mouse plasma or a Tris-bufer that is high in albumin may be used as the buffer in which the transfer of radiolabeled cholesterol esters from HDL to LDL may occur.

Alternatively, other sources of radioactivity may be used to track the CETP activity in this assay.

Alternatively, radiolabeled-LDL may be used in this assay.

ASSAY OF CETP ACTIVITY *IN VIVO*.

Syrian Golden Hamsters, which express endogenous CETP, are used to assess the activity of the compounds *in vivo*. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood can be obtained. CETP activity is determined by a method similar to that described for the *in vitro* CETP activity assay, except that plasma from treated animals is used as the CETP source in the assay.

A strain of transgenic mice that express human CETP (Taconic, Germantown, NY) are used to test compounds of this invention. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood can be obtained. CETP activity is determined by a method similar to that described for the *in vitro* CETP activity assay, except that plasma from treated animals is used as the CETP source in the assay.

Alternatively, a strain of transgenic mice that express both human CETP and human apolipoprotein A-1 (Taconic, Germantown, NY) are used to test compounds of this invention. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood is obtained. CETP activity is determined by a method similar to that described for the *in*

vitro CETP activity assay, except that plasma from treated animals is used as the CETP source in the assay.

ASSAY OF PLASMA LIPIDS *IN VIVO*.

The efficacy of these compounds *in vivo* can also be determined utilizing Syrian Golden Hamsters. The compounds can be tested in hamsters made hypercholesterolemic by feeding a high fat high cholesterol diet for a minimum of two weeks or in non-hypercholesterolemic hamsters fed normal chow for two weeks. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions are analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Alternatively, a strain of transgenic mice that express human CETP (Taconic, Germantown, NY) are used to test the efficacy of the compounds of this invention. The hCETP mice can be made hypercholesterolemic by feeding a high fat chow diet such as TD 88051, as described by Nishina et al. (J Lipid Res., 31, 859-869 (1990)) for at least two weeks before the start of the study. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions **ARE** analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Alternatively, a strain of transgenic mice that express both human CETP and human apolipoprotein A-1 (Taconic, Germantown, NY) are used to test the efficacy of the compounds of this invention. The mice that express both human CETP and human apolipoprotein A1 can be made hypercholesterolemic by feeding a high fat chow diet such as TD 88051, as described by Nishina et al. (J Lipid Res., 31, 859-869 (1990)) for at least two weeks before the start of the study. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions can be analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Method of Treatment

As used herein, the term "effective amount" means an amount of compound of the present invention, i.e., formula I, which is capable of alleviating the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 0.01 mg to about 100 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 1 mg to about 250 mg/day.

The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Thus, another aspect of the present invention is a pharmaceutical composition comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, solvate, prodrug, enantiomer or prodrug thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent, excipients and salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations of the present invention can be prepared by procedures known in the art using well-known and readily available ingredients. For example, the compounds of formula I can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents

for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Compounds of formula I, generally, will be administered in a convenient formulation as determined by the attending physician. The following formulation examples are only illustrative and are not intended to limit the scope of the present invention.

Formulations

In the formulations which follow, "Active Ingredient" means a compound of formula I, a salt, solvate, racemate, enantiomer diastereomer or mixture of diastereomers, or prodrug thereof, or a combination of a compound of formula I and other effective agent for the treatment or prevention of dyslipidemia or atherosclerosis.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The formulation above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	2.5 - 1000
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 2.5 - 1000 mg of active ingredient are made up as follows:

Formulation 3: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	25 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders that are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The

sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules, which after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

Formulation 5: Aerosol

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30° C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Formulation 6: Intravenous Solution

Ingredient	Quantity
Active ingredient	50 mg
Isotonic saline	1,000 mL

The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

Examples

Example 1

Synthesis of 5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester.

Step 1. Preparation of 2-(Toluene-4-sulfonylamino)-benzoic acid methyl ester.

To a mixture of 2-Amino-benzoic acid methyl ester (900 g, 6 mol) in pyridine (6 L) was added p-Toluenesulfonyl chloride (1500 g, 7.5 mol). The mixture was stirred overnight at room temperature. The mixture was poured into ice water, and the resultant precipitates were collected by filtration. The filtrates were dissolved in CH₂Cl₂, and the solution was washed with diluted HCl, H₂O, and dried over MgSO₄. The residue thus obtained was crystallized from ethanol to give 2-(Toluene-4-sulfonylamino)-benzoic acid methyl ester (1454 g, 80%).

Step 2. Preparation of 2-[(3-Ethoxycarbonyl-propyl)-(toluene-4-sulfonyl)-amino]-benzoic acid methyl ester.

A mixture of 2-(Toluene-4-sulfonylamino)-benzoic acid methyl ester (1000 g, 3.27 mol), ethyl 4-bromobutyrate (639 g, 3.45 mol) in 2-butanone (5.6 L) was heated at reflux for 24 hours. After the reaction was completed, the mixture was poured into ice-water, and the resultant precipitates were collected by filtration. The filtrates were washed with ethyl acetate to give 2-[(3-Ethoxycarbonyl-propyl)-(toluene-4-sulfonyl)-amino]-benzoic acid methyl ester (890 g, 65%).

Step 3. Preparation of 5-Oxo-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-4-carboxylic acid ethyl ester.

To a heated mixture of potassium t-butoxide (371 g, 3.58 mol) in toluene (4 l) at 70° C was added 2-[(3-Ethoxycarbonyl-propyl)-(toluene-4-sulfonyl)-amino]-benzoic acid methyl ester (750 g, 1.79 mol). After the addition was completed, the mixture was cooled to room temperature then poured into ice-water. The extraction with CH₂Cl₂ was successively done, and organic layer was dried over MgSO₄ and concentrated under reduced pressure to afford crude compound 5-Oxo-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-4-carboxylic acid ethyl ester (450 g) as a mixture of Me and Et esters.

Step 4. Preparation of 1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-benzo[b]azepin-5-one.

To the mixture of 5-Oxo-1-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepine-4-carboxylic acid ethyl ester thus obtained, were added AcOH (2.4 l), conc.HCl (800 ml) and H₂O (240 ml). The mixture was heated at reflux for 5h and poured into ice-water. The pH was adjusted to about 7-8 by adding diluted aqueous NaOH. The mixture was extracted with CH₂Cl₂. The organic layer was separated, dried over MgSO₄, concentrated, and the residue was crystallized from the mixture (4:1 n-hexane:AcOEt) to

give 1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-benzo[b]azepin-5-one (278 g, 60%) as a white powder.

Step 5. Preparation of 1,2,3,4-Tetrahydro-benzo[b]azepin-5-one.

To preheated polyphosphoric acid (PPA, 220 g) at 70-80° C was added 1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-benzo[b]azepin-5-one (50.0 g, 0.16 mol). The mixture was stirred for 3.0 h at the same temperature, then poured into ice-water. After the pH was adjusted to about 8-9 by adding aq NaOH, the mixture was extracted with ethyl acetate. The organic layer was separated, dried over MgSO₄, and concentrated. The residue was purified by silica gel column chromatography (eluent, 3:1 n-hexanes: ethyl acetate) to give 1,2,3,4-Tetrahydro-benzo[b]azepin-5-one (22g).

Step 6. Preparation of 5-Oxo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester.

To a cooled (0° C) solution of 1,2,3,4-Tetrahydro-benzo[b]azepin-5-one (1.5 g, 9.3 mmol) and pyridine (2.26 ml, 27.9 mmol) in dichloromethane (30 ml) was added 1M isopropylchloroformate (solution in toluene) dropwise over 10 minutes. After addition was completed, the mixture was removed from the cold bath and stirred for 18 hours at room temperature. The mixture was cooled to 0° C, then treated with aqueous 1N NaOH and stirred for 30 minutes. After layer separation, the aqueous layer was extracted with dichloromethane. The combined organic phases were washed with 1N HCl, saturated aqueous NaHCO₃, brine, then dried (Na₂SO₄) and concentrated to an oil. Purification by silica gel chromatography (eluent, 3:1 n-hexanes:ethyl acetate) provided 5-Oxo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester (1.91 g).

Step 7. Preparation of 5-(3,5-Bis-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester.

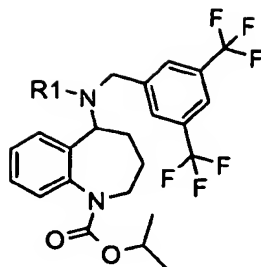
A mixture of 5-Oxo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester (283 mg, 1.14mmol), 3,5-Bis(trifluoromethyl)benzylamine (304 mg,

1.25mmol) and titanium(IV)isopropoxide (0.43 ml, 1.43 mmol) was stirred at room temperature for 6 hours. The mixture was diluted with methanol (5 ml) and treated with sodium borohydride (65 mg, 1.71 mmol), then stirred at room temperature for 18 hours. The mixture was treated with 0.1 N NaOH (25 ml) and stirred for 10 minutes, then filtered through Celite. The filtered residue was washed successively with diethyl ether and dichloromethane. The filtrate was transferred to a separatory funnel and the organic layer was separated, dried (Na₂SO₄) and concentrated to provide crude 5-(3,5-Bis-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester which was elaborated without purification.

Step 8. Preparation of 5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester.

A solution of crude 5-(3,5-Bis-trifluoromethyl-benzylamino)-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester (200 mg, 0.42 mmol) and pyridine (0.85 ml, 10.5 mmol) in dichloromethane (2 ml) at room temperature was treated with acetic anhydride (0.79 ml, 8.4 mmol) via dropwise addition over 4 minutes. The mixture was stirred at room temperature for 20 hours. The mixture was cooled (0° C) and treated with 1N NaOH and stirred for 30 minutes. The aqueous layer was extracted with dichloromethane. The combined organic phases were washed with 1N HCl, dried (Na₂SO₄) and concentrated to an oil. Purification by silica gel chromatography (eluent, 2:1 n-hexanes:ethyl acetate) provided 5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester (144 mg).

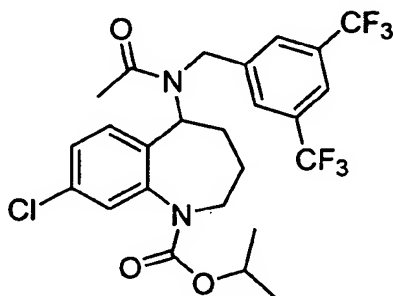
Additional compounds were prepared utilizing this same methodology in which R1 is variable and is introduced by replacement of acetic anhydride with alternative reagents in Example 1, Step 8 for the synthesis of 5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester.



Example #	Reagent	R ¹	MS (ES+)
Example 2	methylchloroformate	methoxycarbonyl	533 (M+H)

Example 3

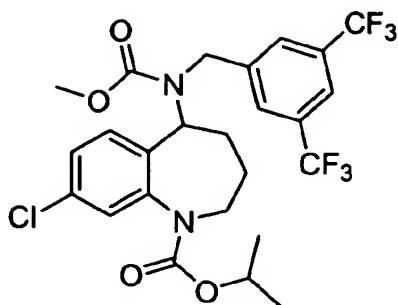
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-chloro-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester



The titled compounds was prepared following the procedures described in **Example 1** by replacing 2-Amino-benzoic acid methyl ester with 2-Amino-4-chloro-benzoic acid methyl ester in **Example 1**, step 1. MS (ES⁺): 551 (M+H).

Example 4

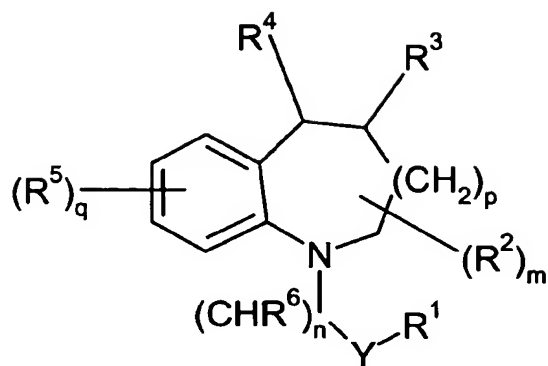
5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-8-chloro-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester



The titled compounds was prepared following the procedures described in **Example 1** by replacing 2-Amino-benzoic acid methyl ester with 2-Amino-4-chloro-benzoic acid methyl ester in **Example 1**, step 1 as well as replacing acetic anhydride with methyl chloroformate in **Example 1**, Step 8. MS (ES⁺): 567 (M+H).

We claim:

1. A compound of formula I



wherein

n is 0, 1, 2, or 3;

m is 0, 1, 2, or 3;

p is 1 or 2;

q is 0, 1, 2, or 3;

Y is a bond, $C=O$, or $S(O)_p$

R^1 is selected from a group consisting of hydroxy, C_1 - C_6 alkyl, aryl, C_2 - C_6 alkenyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylheterocyclic, C_3 - C_8 cycloalkyl, C_1 - C_6 alkylaryl, heterocyclyl, C_1 - C_6 alkoxy, aryloxy, $-OC_2$ - C_6 alkenyl, $-OC_1$ - C_6 haloalkyl, $-OC_1$ - C_6 alkylheterocyclic, $-OC_3$ - C_8 cycloalkyl, $-NR^7R^8$ and $-OC_1$ - C_6 alkylaryl, $-O$ -heterocyclic, and $-OC_1$ - C_6 alkylheterocyclic; provided that R^1 is not hydroxy when Y is $S(O)_p$;

R^2 is bound only to carbon atoms and is a group independently selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, heterocyclyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl; wherein the alkyl group is optionally substituted by alkyloxy, aryloxy, haloalkyl, heterocyclyl;

R^3 is hydrogen or a group represented by the formula $-NR^9R^{10}$;

R^4 is hydrogen or a group represented by the formula $-NR^9R^{10}$; provided that R^3 and R^4 are not simultaneously hydrogen or $-NR^9R^{10}$;

R^5 is selected from a group consisting of hydrogen, hydroxy, C_1 - C_6 haloalkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 alkylaryl, C_1 - C_6 alkylheterocyclic, aryl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 -

C₆ alkoxy, aryloxy, -OC₂-C₆ alkenyl, -OC₁-C₆ haloalkyl, -NR⁷R⁸, and -OC₁-C₆ alkylaryl wherein C₁-C₆ alkyl is optionally substituted by alkyloxy, aryloxy;

R⁶ is independently selected from a group consisting of hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl hydroxy, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, aryloxy, -OC₂-C₆ alkenyl, -OC₁-C₆ haloalkyl, C₁-C₆ alkylNR⁷R⁸, C₃-C₈ cycloalkyl, and C₁-C₆ alkylcycloalkyl;

R⁷ and R⁸ are independently selected from a group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₃-C₈ cycloalkyl, heterocyclic, aryl, C₁-C₆ alkylaryl, wherein each alkyl, or aryl group is optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆ alkylheterocyclic, C₁-C₆ haloalkyl, and NR¹¹R¹², or R⁷ and R⁸ combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional hetero-atoms selected from oxygen, nitrogen or sulfur and may be optionally substituted with oxo, or C₁-C₆ alkyl;

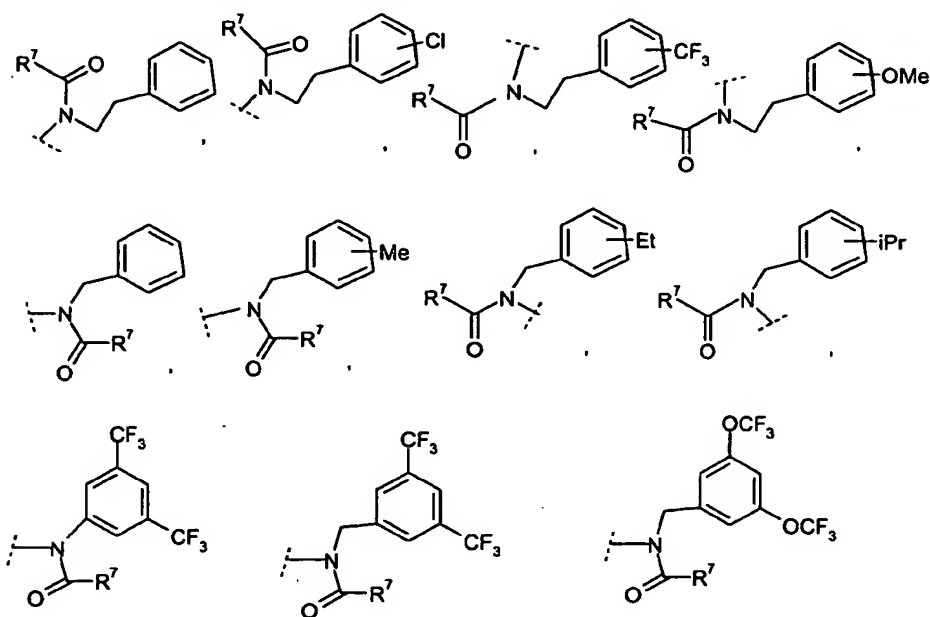
R⁹ is the group COR⁷ or S(O)_pR⁷ wherein R⁷ is as defined above.

R¹⁰ is selected from the group consisting of C₁-C₆ alkylaryl, C₂-C₆ alkenylaryl, C₂-C₆ alkynylaryl, C₁-C₆ alkylheterocyclic, C₁-C₆ alkylcycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkyl-O-C₁-C₆ alkylaryl, C₁-C₆ alkyl-NR²-C₁-C₆ alkylaryl, aryl, and wherein each alkyl, alkenyl, cycloalkyl, aryl, or heterocyclic group are optionally substituted with 1-3 groups independently selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₁-C₆ haloalkyl, halogen, C₁-C₆ alkoxy, aryloxy, C₁-C₆ alkenyloxy, C₁-C₆ haloalkoxyalkyl, NR⁷R⁸ and -OC₁-C₆ alkylaryl;

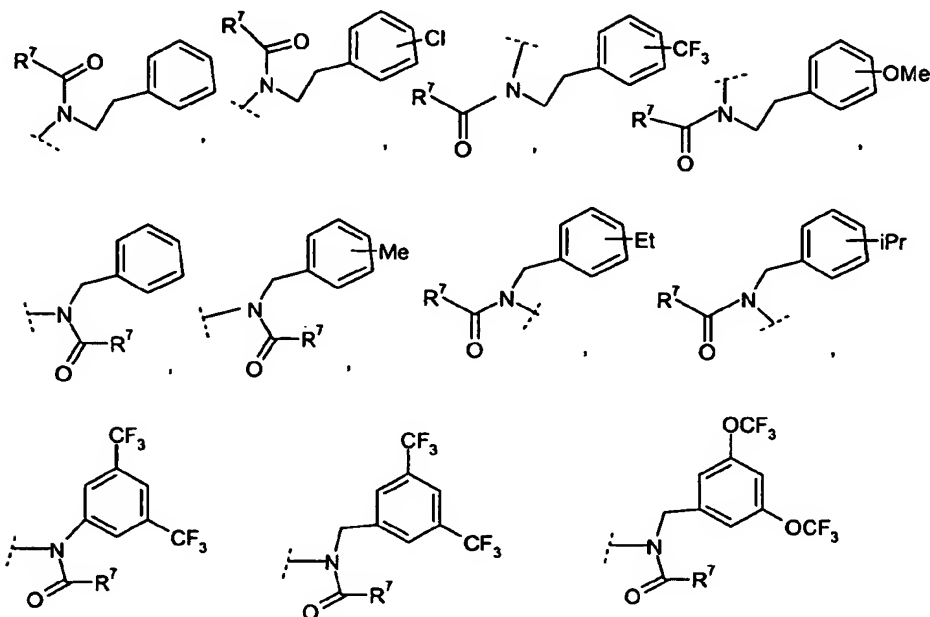
R¹¹ and R¹² are independently selected from a group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₃-C₈ cycloalkyl, heterocyclic, aryl, C₁-C₆ alkylaryl, wherein each aryl group is optionally substituted with 1-3 groups independently selected from halogen, C₁-C₆ alkylheterocyclic, and C₁-C₆ haloalkyl, or R¹¹ and R¹² combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen or sulfur and is optionally substituted with oxo, or C₁-C₆ alkyl; or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

2. A compound according to Claim 1 wherein R¹ is selected from a group consisting of C₁-C₆ alkoxy, aryloxy, -OC₂-C₆ alkenyl, -OC₁-C₆ haloalkyl, -OC₃-C₈ cycloalkyl, -OC₁-C₆ alkylaryl, and -OC₁-C₆ alkylheterocyclic.

3. A compound according to Claim 1 wherein p is 1.
4. A compound of claim 1 wherein p is 2.
5. A compound of claim 1, wherein p is 1 or 2; n is 0 or 1; m is 0, and q is 0.
6. A compound according to Claim 1 wherein n, m, and q are independently 0, or 1.
7. The compound according to Claim 1 wherein R^4 is hydrogen and R^3 is selected from the group consisting of:



8. A compound according to Claim 1 wherein R^3 is hydrogen and R^4 is selected from the group consisting of:



9. A compound selected from the group consisting of:

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,

5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-bromo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,

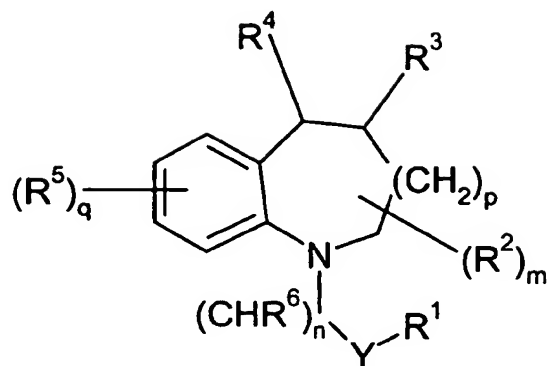
5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-7-bromo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-bromo-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-methoxy-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid ethyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-fluoro-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-4,4-dimethyl-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
6-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-trifluoromethyl-3,4,5,6-tetrahydro-2H-benzo[b]azocine-1-carboxylic acid isopropyl ester,
6-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-9-trifluoromethyl-3,4,5,6-tetrahydro-2H-benzo[b]azocine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-9-trifluoromethyl-3,4,5,6-tetrahydro-2H-benzo[b]azocine-1-carboxylic acid isopropyl ester,
4-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[Acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-8-chloro-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester,
5-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-8-chloro-2,3,4,5-tetrahydro-benzo[b]azepine-1-carboxylic acid isopropyl ester, or a pharmaceutically acceptable salt, solvate enantiomer or diastereomer or mixture thereof.

10. A method of antagonizing CETP activity comprising administering a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof to a patient in need thereof.

11. A method of treating or preventing dyslipidemia comprising administering a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers thereof, to a patient in need thereof.
12. A method of treating or preventing atherosclerosis comprising administering a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient.
13. A method according to Claim 10, wherein the down-regulation of CETP activity results in a decrease in LDL- cholesterol.
14. A method of lowering plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient in need thereof.
15. A method of treating and/or preventing the pathological sequelae due to high levels of plasma LDL-cholesterol in a mammal comprising administering an effective dose of a compound of formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers to a patient in need thereof.
16. A pharmaceutical formulation comprising a compound according to Claim 1 and a carrier, diluent and/or excipient.
17. Use of a compound of formula I for the manufacture of a medicament for treating and/or preventing atherosclerosis in a mammal comprising administering an effective dose of a compound of formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient in need thereof.

Abstract

Compounds of formula I



wherein n , m , p , q , y , R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as defined herein and their pharmaceutical compositions and methods of use are disclosed as useful for treating atherosclerosis and its sequelae.

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